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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/625,963	07/26/2000	Hans Josef Stauss	ICI 101	8595

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EXAMINER	
DECLOUX, AMY M	
ART UNIT	**PAPER NUMBER**
1644	23

DATE MAILED: 05/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N. 09/625,963	Applicant(s) STAUSS ET AL.	
	Examiner Amy M. DeCloux	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2-18-03 & 11-14-02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,7,15,19 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,5,15,19 and 44* is/are rejected.

7)☒ Claim(s) *7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 July 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: Notice to Comply with Sequence Requirements.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11-14-02 and 2-18-03 have been entered.

Claims 1, 5, 7, 15, 19 and 44 are pending.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper". Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. Specifically several references are listed on pages 68-73.

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Sequences are disclosed in the specification that lack SEQ ID NO: tags. Specifically sequences without sequence tags are disclosed on page 59, lines 2-4 and lines 6-7. Also lines 1, 3 and 5 of the Abstract contain sequences lacking SEQ ID NO: tags. Applicants are required to resubmit a substitute disk and paper copy of the sequences according to the attached "Notice to Comply with the Sequence Rules." Applicant is reminded of the sequence rules which require a submission for all sequences of more than 9 nucleotides or 3 amino acids (see 37 C.F.R. 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

MAINTAINED Claims 1, 5, 15, 19 and 44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 5, 15, 19 and 44 encompass a peptide having at least nine but fewer than 100 amino acids, comprising the amino acid sequence of SEQ ID NO:1, (RMFPNAPYL), a pharmaceutical composition thereof, and a vaccine comprising said peptide, wherein said peptide is capable of binding to HLA-A0201 or is capable of being processed by an antigen presenting cell so that a fragment is produced which is able to bind HLA-A201.

The instant disclosure of "a peptide comprising the amino acid sequence of SEQ ID NO:1" does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera. By reciting a peptide that has at least nine but fewer than 100 amino acids, said peptide can also encompass an indeterminate number and type of additional amino acids, in addition to the amino acids recited in SEQ ID NO:1.

It is noted that though the claimed invention is directed to peptides and not cDNA, the principle of the following still holds for said peptides: a description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly&Co.*, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

With regard to the representative number of species, only one species is disclosed that comprises SEQ ID NO:1 and is capable of binding HLA-A0201, and said disclosed species is that of a peptide consisting of SEQ ID NO:1. The instant specification discloses cancers such as some leukemias that over express WT-1 (comprising SEQ ID NO:1), which the instant specification discloses as being derived from human WT-1 transcription factor. However no fragments of WT-1 comprising SEQ ID NO:1, other than SEQ ID NO:1 itself, are described in the instant specification. Further, the prior art does not provide compensatory structural or correlative teachings to enable one of skill to identify a peptide having at least nine but fewer than 100 amino acids, comprising the amino acid sequence of SEQ ID NO:1, that binds HLA-A0201 other than SEQ ID NO:1 (RMFPNAPYL) itself.

Given the indefiniteness of the number and type of additional amino acids that may be encompassed by the peptide of the instant claims, the peptide, pharmaceutical composition thereof, and a vaccine comprising said peptide, the structure of "a peptide _having at least nine but fewer than 100 amino acids, comprising the amino acid sequence of SEQ ID NO:1" is not conventional in the art and one of skill in the art would not recognize from the disclosure that applicant was in possession of the genus of peptides encompassed by the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.)

Response to Arguments

Applicant's arguments filed 11-14-2002 have been fully considered but they are not persuasive.

Applicant traverses the rejection as it applies to the claims as amended. The traversal appears to be directed to the contention that the term "comprising" in the instant claims does not refer to an indeterminate number and type of amino acids because said peptide has at least 9 but fewer than 100 amino acids, and because the sequences that flank SEQ ID NO:1 motif is not important to the correct processing of the polypeptide. Applicant further asserts that an APC is able to correctly process virtually all proteins it is exposed to, apparently based on a quotation from an attached reference by Shastri et al wherein said quote states that "these studies provide compelling evidence for amino peptidase trimming in the ER as the key event in the antigen processing pathway". The examiner notes that said Shastri article teaches on page 483 that peptides with the amino terminus of XP can not be trimmed by aminopeptidase in the ER and that said Shastri reference teaches that the C terminal end cutting occurs in the cytoplasm by proteosomes according to three major cleavage specificities of the proteosome, page 479, column 1, lines 1-12. Therefore, said sequences that flank SEQ ID NO:1 are important, and the specification does not provide adequate description of any fragments of a peptide of at least 9 but fewer than 100 amino acids that comprises SEQ ID NO:1, wherein said peptide is capable of binding to HLA-A0201 or is capable of being processed by an antigen presenting cell so that a fragment is produced which is able to bind HLA-A201, other than SEQ ID NO:1 itself.

MAINTAINED Claims 1, 5, 15, 19 and 44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 5, 15, 19 and 44 encompass a peptide having at least nine but fewer than 100 amino acids, comprising the amino acid sequence of SEQ ID NO:1, (RMFPNAPYL), a pharmaceutical composition thereof, and a vaccine comprising said peptide, wherein said peptide is capable of binding to HLA-A0201 or is capable of being processed by an antigen presenting cell so that a fragment is produced which is able to bind HLA-A201.

The instant claims are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the recitation of a vaccine for any tumor cell, including those that over express WT-1. Neither does the instant specification provide enablement for how to make and use a peptide having at least nine but fewer than 100 amino acids, comprising the amino acid sequence of SEQ ID NO:1, (RMFPNAPYL), a pharmaceutical composition thereof, and a vaccine comprising said peptide, wherein said peptide

is capable of binding to HLA-A0201 or is capable of being processed by an antigen presenting cell so that a fragment is produced which is able to bind HLA-A201, other than a peptide consisting of SEQ ID NO:1 itself.

As such, the specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed in the instant claims without an undue amount of experimentation. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of peptides broadly encompassed by the claims, nor with the large number of tumors.

The instant specification discloses cancers such as some leukemias that over express WT-1 (comprising SEQ ID NO:1), which the instant specification discloses as being derived from human WT-1 transcription factor. The instant specification also discloses on page 54 and in Figures 5 & 6, that the peptide consisting of SEQ ID NO:1 is i) presented by leukemic tumor cell lines that over express WT-1 and express HLA-A2, ii) that CTL directed to the peptide consisting of the amino acid sequence of SEQ ID NO:1 recognize CD34+ cells from HLA-A0201+ CML patients, as well as CD34+, HLA-A2+ leukemic tumor cell lines.

The instant specification provides insufficient guidance and direction that the recited peptides would be effective as a vaccine against any tumor, including those that over express WT-1 and that express HLA-A2.

The instant specification discloses in Figures 5 and 6 that a peptide of SEQ ID NO:1 is effective in killing cancer cells in vitro, but there is insufficient guidance from the instant disclosure on how to extrapolate from in vitro killing to in vivo killing.

Pages 53-54 disclose that the critical transformation events in CML and AML affect CD34+ cells, and that the in addition to the hallmark t(9;22) chromosomal translocation, the Wt-1 transcription factor is a candidate protein contributing to leukemogenesis, especially in view of its increased expression in CD34+ cells from CML and AML patients and in view of studies showing the in vitro enhancement of proliferation of hematopoietic cells with increased WT-1 expression, and that a recent study suggesting T cells specific for CD34+ progenitor cells are critically important in mediating anti-leukemic effects in CML patients.

However, Janeway teaches that melanoma tumor specific antigens which were recognized by CTL in vitro, were not expanded in vivo, suggesting that said peptides are not immunogenic in vivo (see page 551 of Janeway et al Immunobiology 4th Edition). Therefore, the in vitro data of the instant specification do not provide sufficient guidance and direction to extrapolate that a peptide comprising or consisting of SEQ ID NO:1 is immunogenic in vivo and would be effective as a cancer vaccine, absent evidence to the contrary.

In view of the insufficient guidance and direction from the instant specification and in the art, with regard to the efficacy of the recited peptide, including a peptide consisting of SEQ ID NO:1, as a tumor vaccine, it would require undue experimentation by one of skill in the art to develop a vaccine comprising a peptide comprising SEQ ID NO:1, that would be effective in as a vaccine against any tumor, including tumors that over express WT-1, comprising the use of a peptide consisting of or comprising SEQ ID NO:1.

Further, the instant specification provides insufficient guidance and direction on to make and use a peptide having at least nine but fewer than 100 amino acids, comprising the amino acid sequence of SEQ ID NO:1, (RMFPNAPYL), a pharmaceutical composition thereof, and a vaccine comprising said peptide, wherein said peptide is capable of binding to HLA-

A0201 or is capable of being processed by an antigen presenting cell so that a fragment is produced which is able to bind HLA-A201, other than a peptide consisting of SEQ ID NO:1 itself.

Class I molecules bind short peptides of 8-9 amino acids (see page 121 of Janeway et al). Therefore, the instant specification provides insufficient guidance and direction that a peptide larger than a peptide consisting of SEQ ID NO:1 would bind a class I molecule, as is encompassed by a peptide comprising SEQ ID NO:1 or a fragment thereof.

MHC restricted class I molecules form a pocket in which antigenic peptides fit and consequently bind (see Figure 4.3 and Figure 4.5 of Immunobiology 4th Edition by Janeway et al. (1999)). Therefore, the structure of a peptide must fit a class I molecule.

Page 9 of the specification discloses that if a peptide which is greater than around 12 amino acid residues is used to directly bind to a MHC molecule, it is preferred that the residues that flank the core HLA binding region are ones that do not substantially affect the ability of the peptide to bind to the MHC molecule or present the peptide to the CTL. However, no such residues or peptides are described in the specification. Accordingly, the instant specification provides insufficient guidance and direction that a peptide having at least nine but fewer than 100 amino acids, comprising the amino acid sequence of SEQ ID NO:1, (RMFPNAPYL), other than a peptide consisting of SEQ ID NO:1, will retain a structure that has the ability to fit into the MHC binding pocket.

Therefore, it would take undue experimentation by the skilled artisan to predict which of the recited peptides discussed supra (with the exception of a peptide consisting of SEQ ID NO:1) would bind MHC Class I.

The instant specification provides insufficient guidance and direction regarding which larger peptides having at least nine but fewer than 100 amino acids, comprising the amino acid sequence of SEQ ID NO:1, (RMFPNAPYL), wherein said peptide is capable of being processed by an antigen presenting cell so that a fragment is produced which is able to bind HLA-A201, because the specification provides insufficient guidance regarding which of said peptides will be recognized by a proteosome and processed. The specification discloses on page 6, lines 9-12, that the peptide.... may be processed so that a fragment is produced that may bind an MHC molecule. It is noted that Janeway et al teach that the proteosome is implicated in the production of peptide ligands for MHC Class I molecules and that the proteosome's specificity is determined by its subunits (see page 125). Therefore one of skill would not know how to predict which peptides comprising SEQ ID NO:1 would contain the necessary recognition site for degradation by the proteosomes without further description form the instance specification.

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue experimentation to practice the claimed invention.

Response to Arguments

Applicant's arguments filed 11-14-2002 have been fully considered but they are not persuasive.

Applicant traverses the rejection as it applies to the claims as amended, lists the amendments to claims 1 and 19, and states that the examiner has already indicated that the present specification provides sufficient guidance for vaccines that over-express WT-1 and express HLA-A2 (referring to page 3, third paragraph of Office Action mailed May 20, 2002).

> "Therefore, as stated in the previous office action, the instant specification provides insufficient guidance and direction regarding the effectiveness of the recited peptide consisting of SEQ ID NO:1 as a cancer vaccine on any cancer cells not over expressing WT-1, or not expressing HLA-A2, because the antigen presenting structure would not be present, and/or the peptide antigen would not be present in sufficient quantity.

However, the examiner notes that this alleged sufficient guidance is taken out of context in the sense that the paragraph was trying to convey that over-expression of WT-1 and expression of HLA-A2 were necessary requirements for the vaccine encompassed by the instant claims. Applicant is further directed to page 5, paragraph 7, through page 6, line 10, which expands on the examiner's contention that the in vitro data of the instant specification do not provide sufficient guidance and direction to extrapolate that a peptide comprising or consisting of SEQ ID NO:1 is immunogenic in vivo and would be effective as a cancer vaccine, absent evidence to the contrary.

NEW GROUND OF REJECTION

Claim Rejections - 35 USC § 112

Claims 1, 5, 15, 19 and 44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 5, 15, 19 and 44 are not supported by the specification or by the claims as originally filed. There is no support in the specification or claims as originally filed for the recitation of a peptide wherein said peptide is capable of "being processed by an antigen presenting cell so that a fragment is produced which is able to bind to HLA-A201". There is no written description of the claimed invention in the specification or claims as originally filed. Thus the claimed invention constitutes new matter. Applicant is invited to point out support.

Allowable Subject Matter

Claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy M. DeCloux whose telephone number is 703 306-5821. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 703 308-3973. The fax phone numbers for the organization where this application or proceeding is assigned are 703 872-9306 for regular communications and 703 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308-0196.

Amy DeCloux, Ph.D.
Patent Examiner
April 29, 2003

Patrick J. Nolan, Ph.D.
Primary Patent Examiner
Group 1640

Application No.: 09/625,963

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The Abstract and page 59 disclose sequences which lack SEQ ID NO: tags.

Applicant Must Provide:ONLY IF THE CRF/PAPR COPY SEQUENCE LISTING DOES NOT CONTAIN SAID SEQUENCEs.

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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